Overview of HIV

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Outline

- Background and Epidemiology
- HIV Virology, Transmission, and Pathogenesis
- Acute HIV infection
- HIV Diagnostics
- Pre- and Post-exposure Prophylaxis
- HIV Prevention—Turning the Tide

Historical Perspective

- HIV-1 identified officially 05 JUN 81 (US)
  - CDC MMRW report of 5 unusual Pneumocystis pneumonia cases
- Origin: non-human primates W Africa
  - HIV-1: S Cameroon; evolution of SIV(cpz; chimpanzee)
  - HIV-2 : S Senegal – W Cote d'Ivoire: SIV(smm; sooty managabey)
- Early expectations – vaccine in 2 years (M. Heckler- NIH Director)
- Search for cure and implementation of prevention strategies continues … 2013

HIV

HIV-1 and HIV-2

HIV-1 Group N, O, M

HIV-1 Group M

HIV-2 – 5 Groups

HIV-1

Group N

Cameroon

Group O

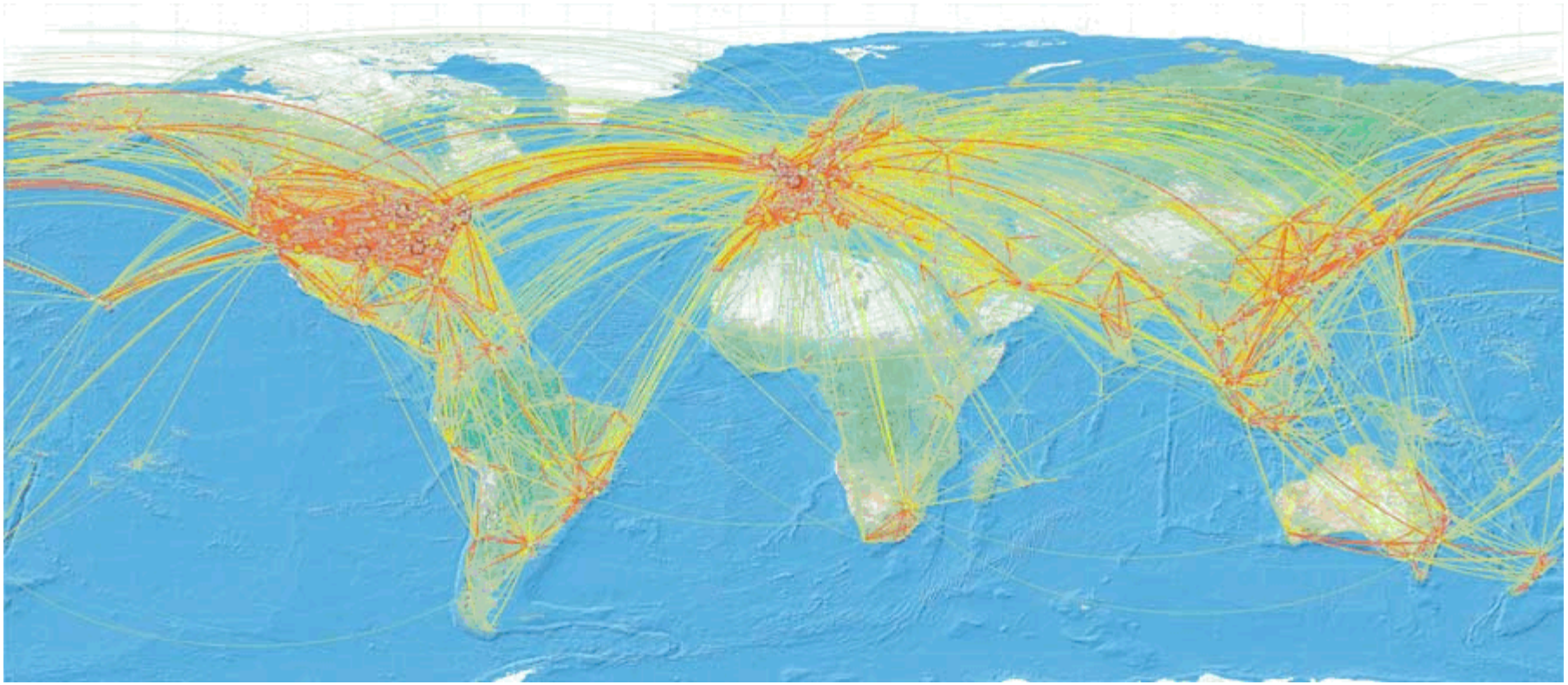
Group M

11 Subtypes

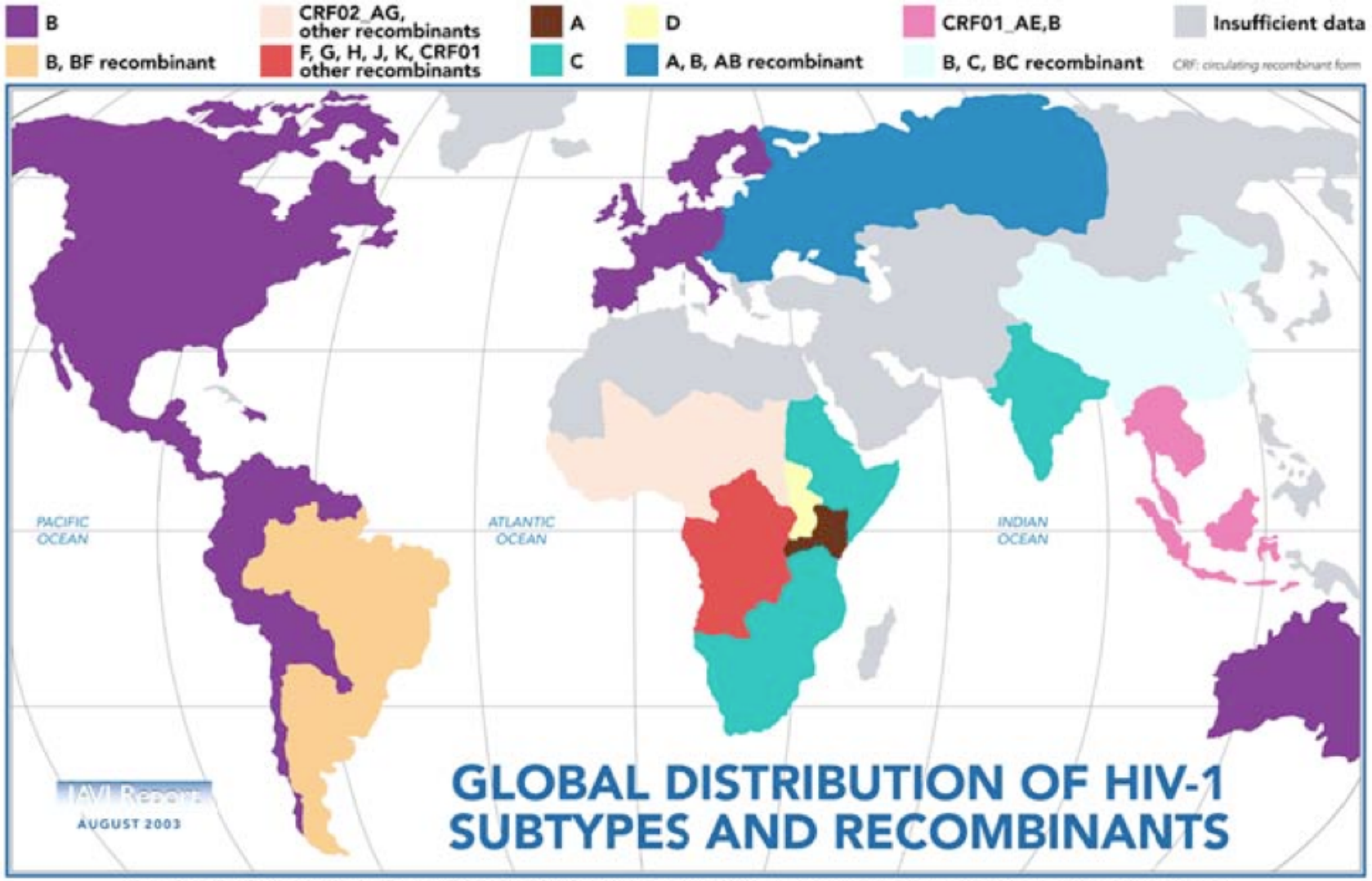
A1, A2, B, C, D, F1, [illegible]

58 Circulating Recombinant Forms (CRF)

Be a virus, see the world



World Wide Distribution HIV-1



Source: Francine E. McCutchan, Henry M. Jackson Foundation (Rockville, Maryland). McCutchan and colleagues are indebted to the many international collaborators who helped develop the data used to generate this map.

Question

- How many new HIV infections occurred in 2011 worldwide?

a) 27,000

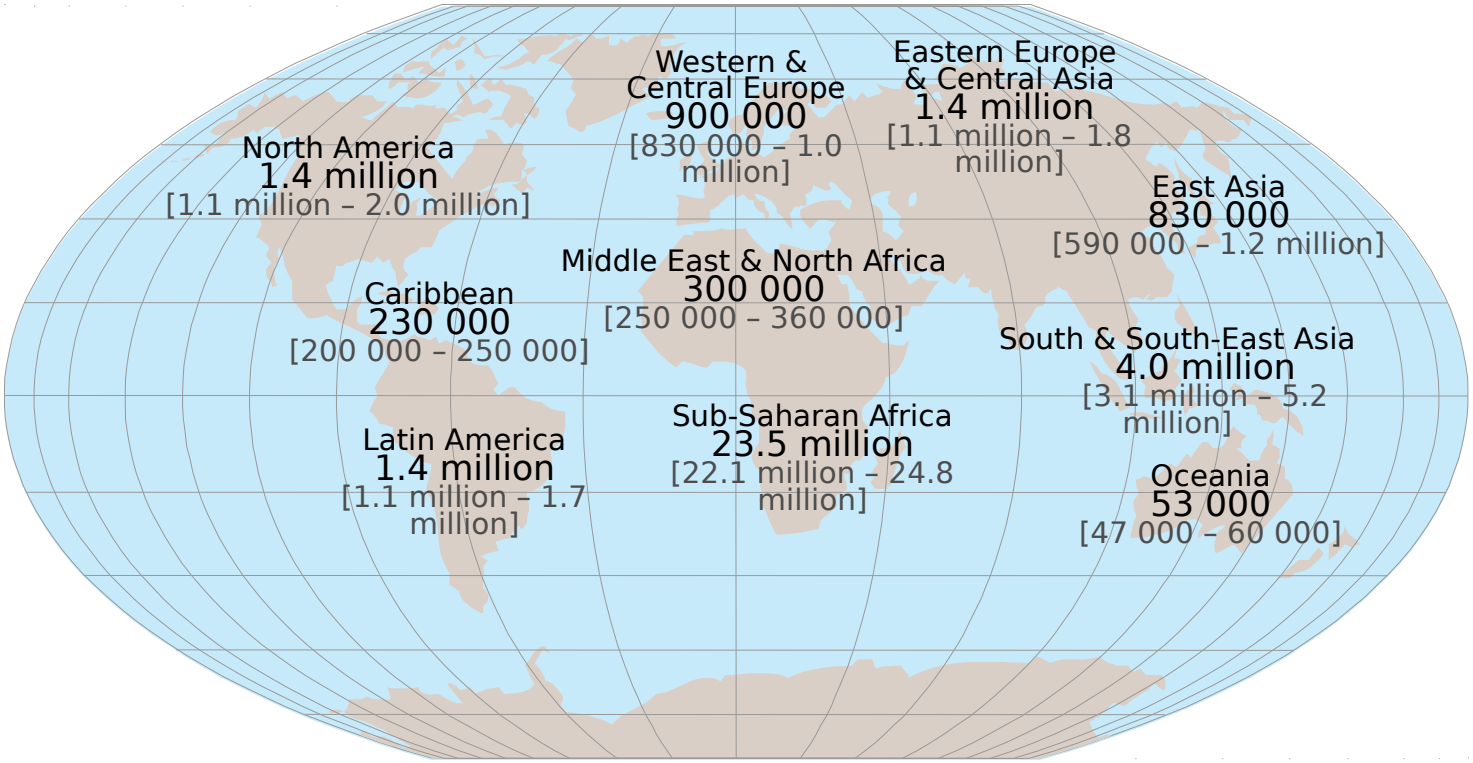
b) 500,000

c) 2,500,000

d) 7,000,000

Adults and children estimated to be living with HIV 2011

New infections: 2,500,000
Estimated Deaths: 1,700,000



Total: 34.0 million [31.4 million – 35.9 million]

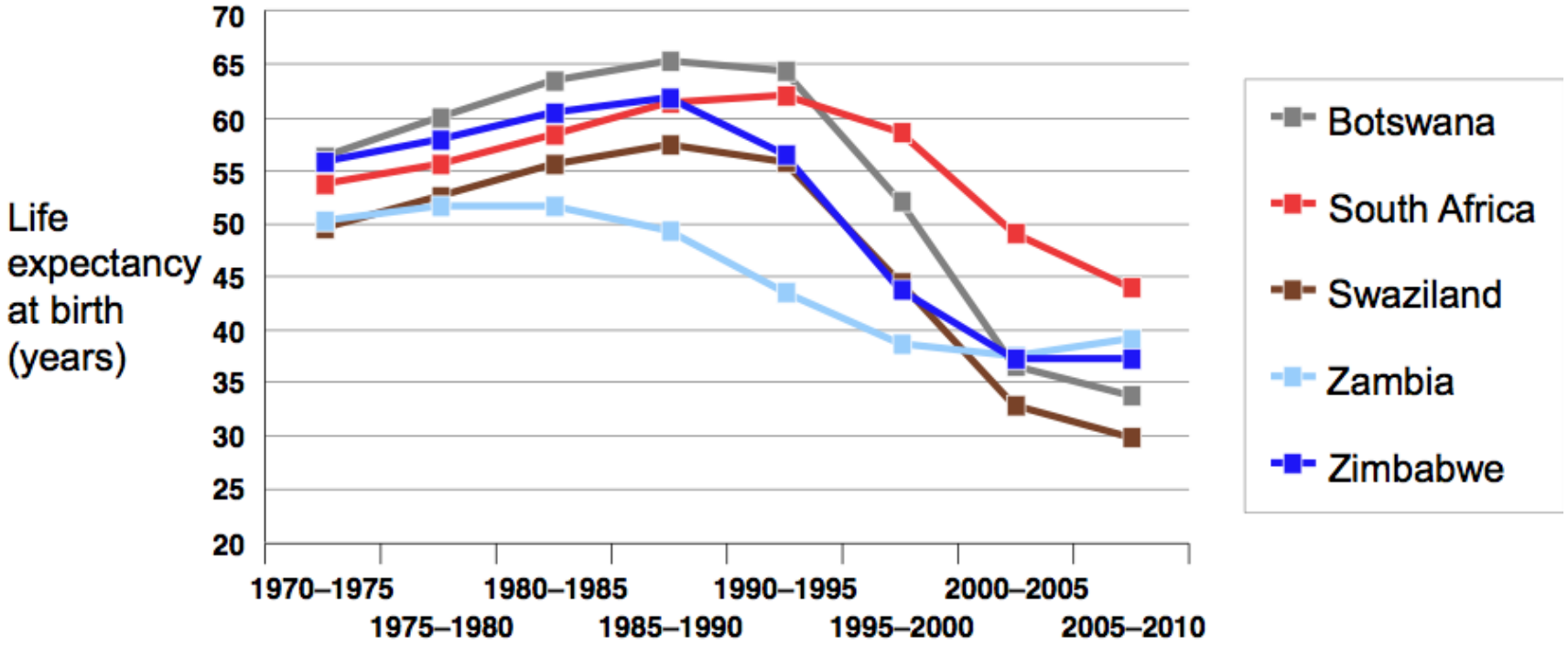
WHO, UNAID 2012

Over 7,000 new HIV Infections a day in 2011

- More than 97% are in low and middle income countries
- ~ 900 are in children under 15 years of age
- ~ 6000 are in adults aged 15 years and older of whom:
  - 47% are among women
  - 41% are among young people (15-24)
- Epi center of epidemic in Sub-Saharan Africa (70%)

AIDS Orphans in the Agape House

Impact of AIDS on life expectancy in five African countries, 1970-2010



Source: United Nations Population Division (2011).

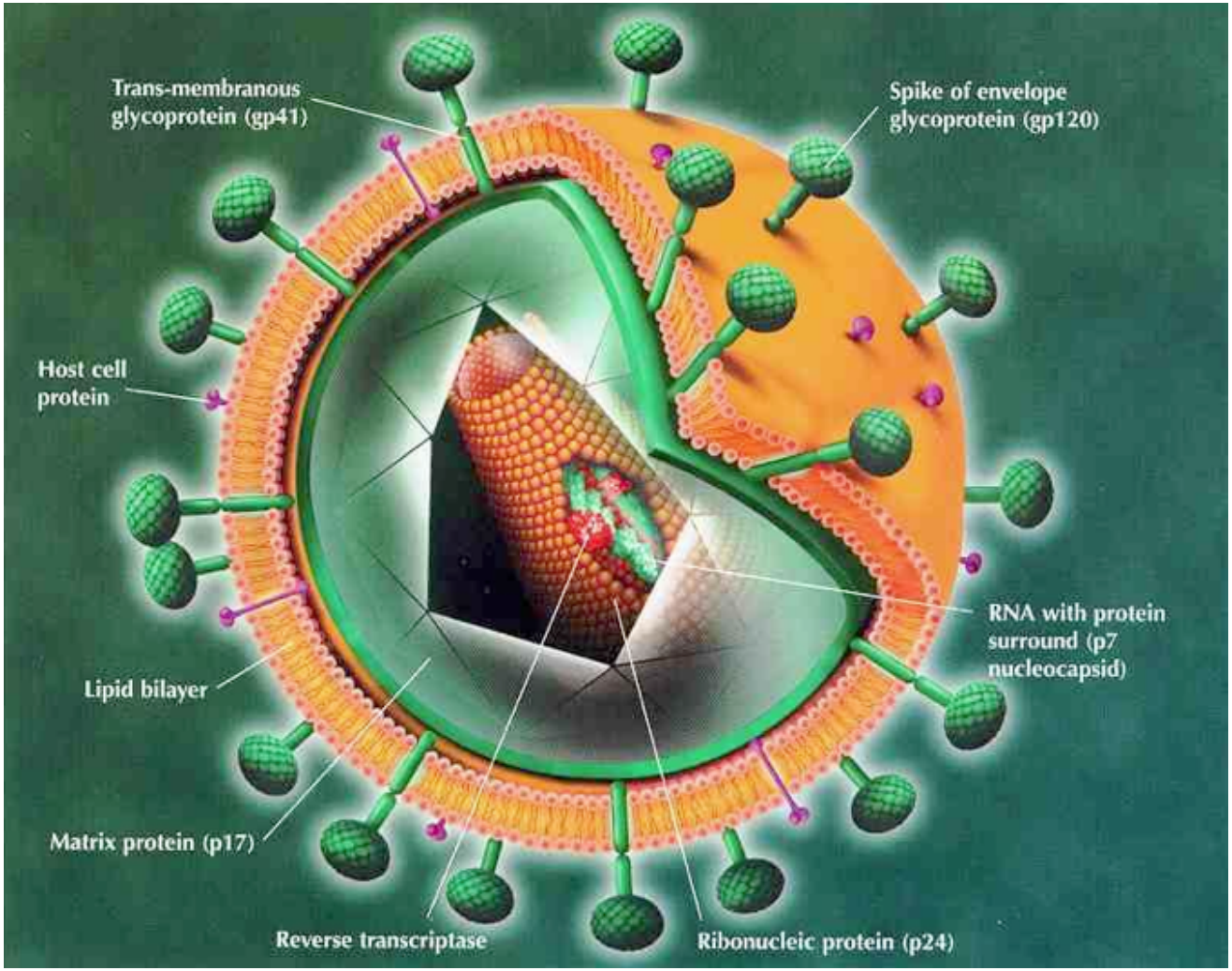
Behavioral-Social Considerations

- Social Stigma
- Global Economics
- Political Instability
- Societal Structure
- Vaccine Induced Seropositivity

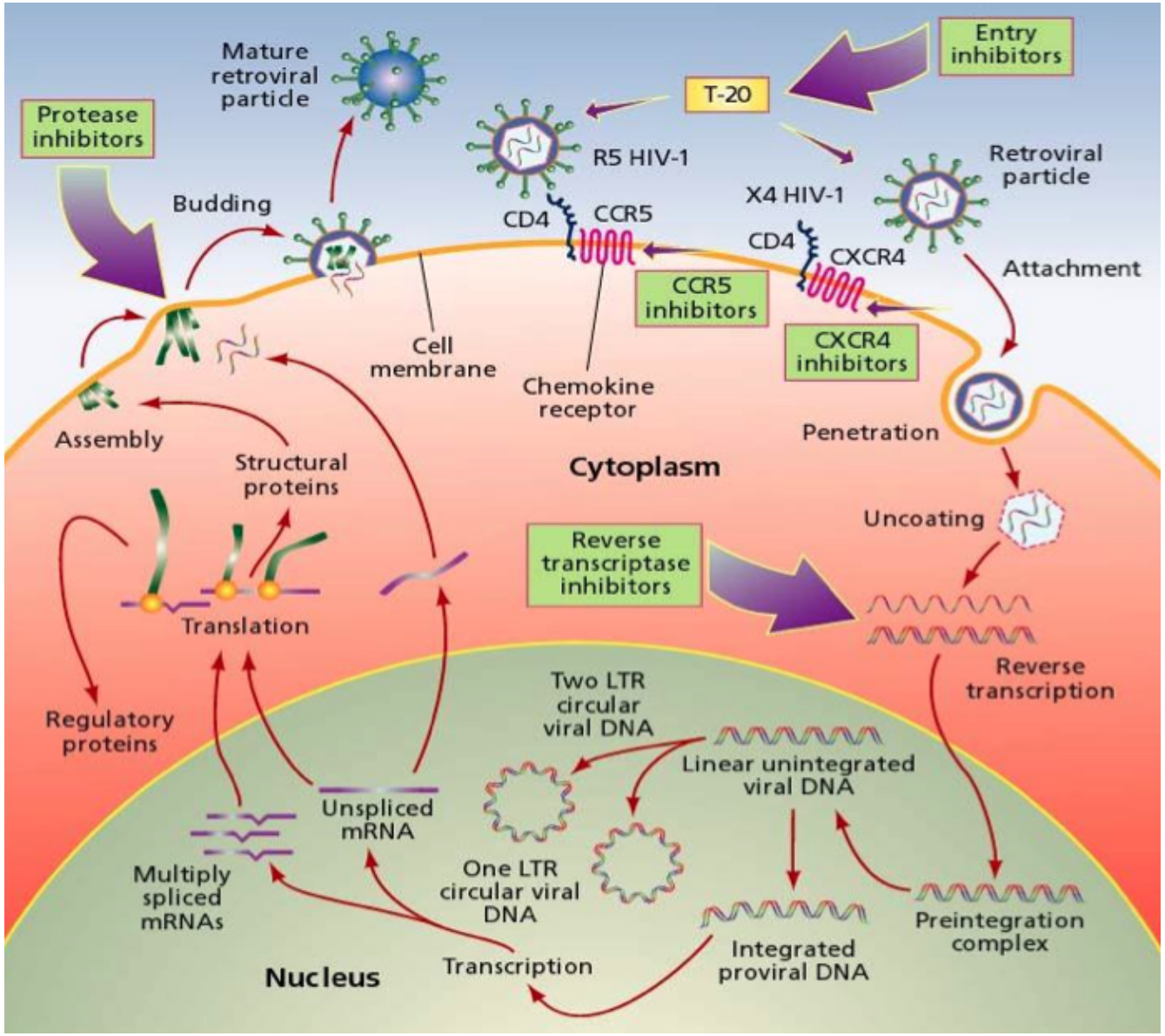
AIDS Orphan, Telegraph 2010

HIV Virology, Transmission and Pathogenesis

HIV Virus Structure



HIV life cycle and mechanisms of anti-virals



Transmission Routes

Unprotected sexual intercourse with an infected partner

Vertical transmission
(from mother to child)
- **in utero**
- **during delivery**
- **breastmilk**

Injection drug use
(rare: infected blood/blood products)

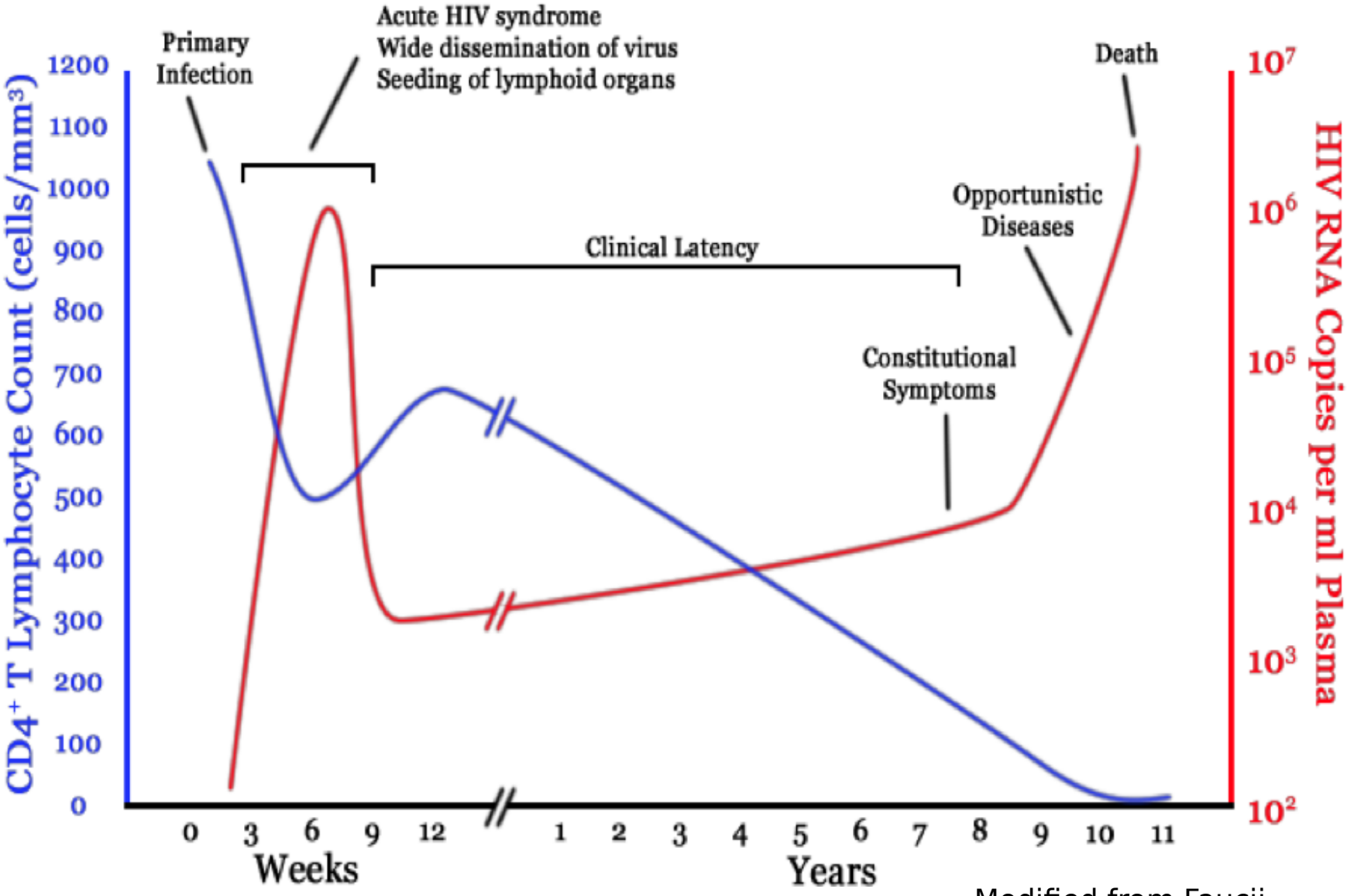
HIV INFECTION

Risk of Specific Exposures

Per Contact Transmission Rate

- Transfusion 95%
- Untreated Perinatal 15-30%
- Occupational:
  - Needle Stick 0.3%
  - Mucous Membrane 0.01-0.1%

Natural History of HIV Infection



Modified from Faucii, 2000

Viral Setpoint and Prognosis

Figure 2. HIV RNA levels 1 year after untreated infection are relatively stable and predict subsequent disease progression. Data are from the Multicenter AIDS Cohort Study.

Acute HIV Infection

Symptoms of Acute HIV Infection

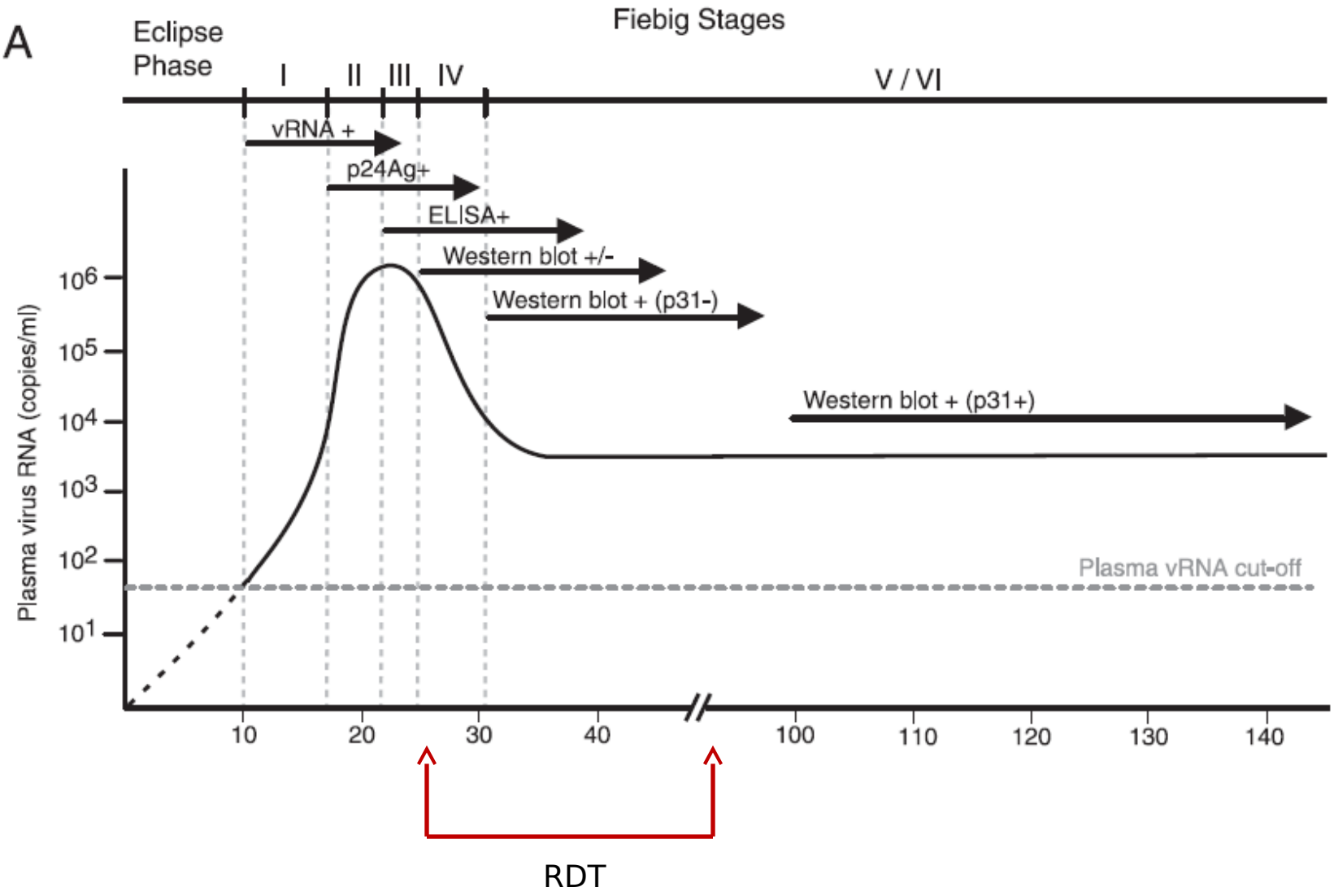
Frequency Symptoms in Acute HIV-1 Infection

- **Fever >80-90%**
- **Fatigue >70-90**
- **Rash >40-80**
- **Headache 32-70**
- **Lymphadenopathy 40-70***
- **Pharyngitis 50-70***
- **Myalgia/arthralgia 50-70**

Kahn and Walker. NEJM 1998. 339(1):33-9.
*highest in younger patients, Vanhems. JAIDS 2002;31:318-321.

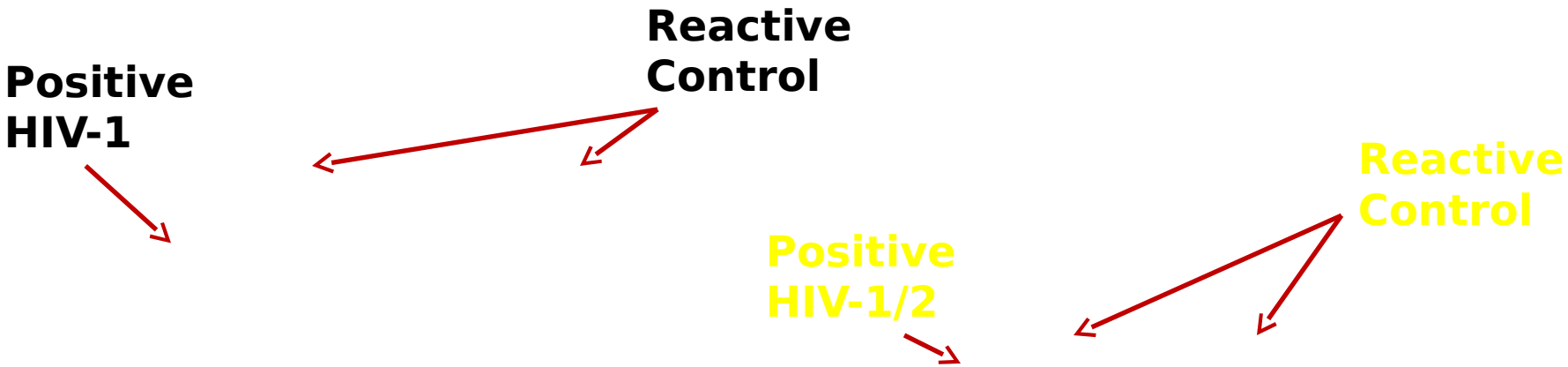
HIV Diagnostics

HIV Infection Staging



Rapid Immunoasay - RIA

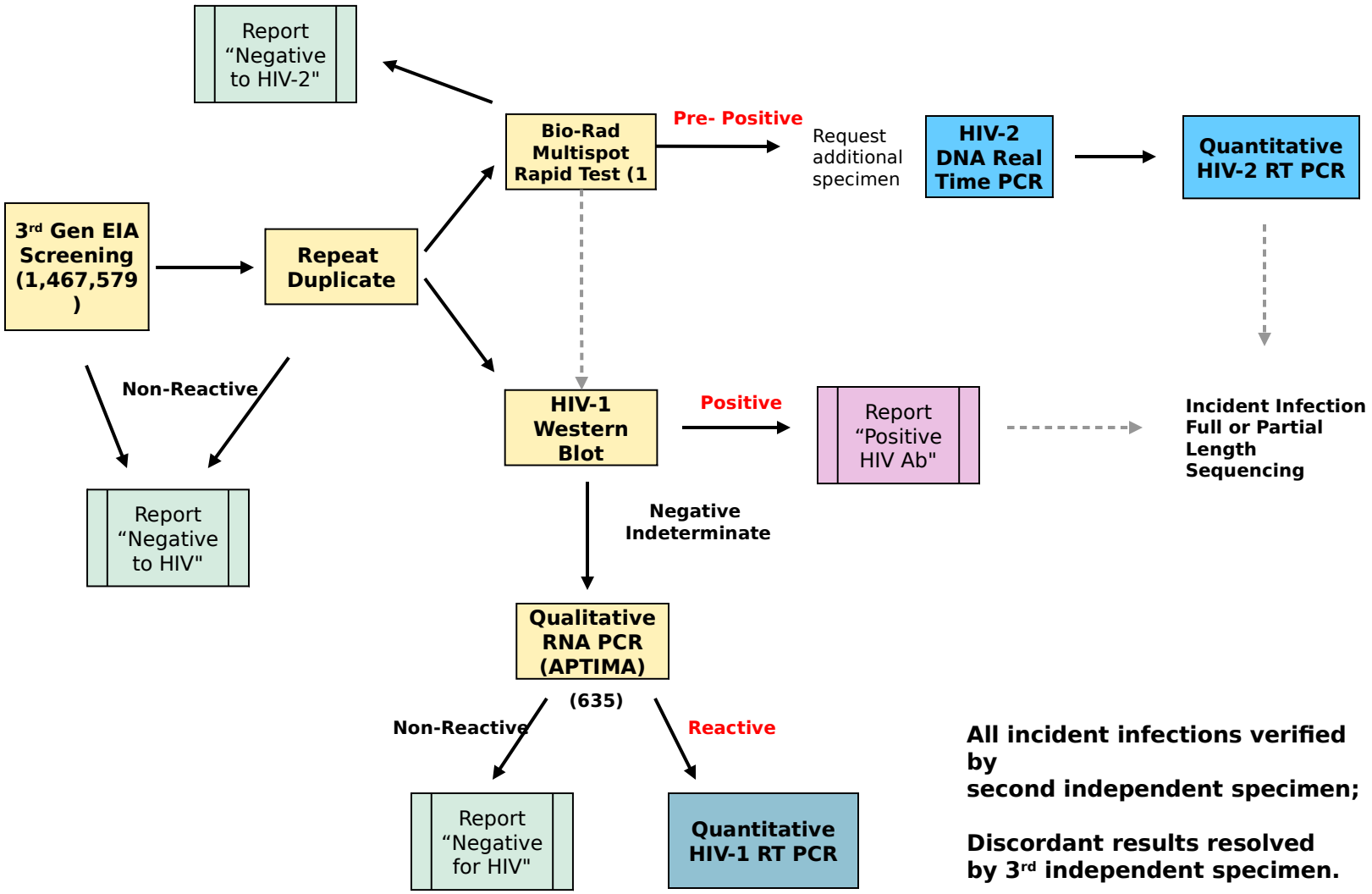
- Uni-Gold Recombigen and OraQuick Advance HIV-1/2



Results in 10-12 minutes

Results in 20 minutes

US Army HIV Diagnostic Algorithm

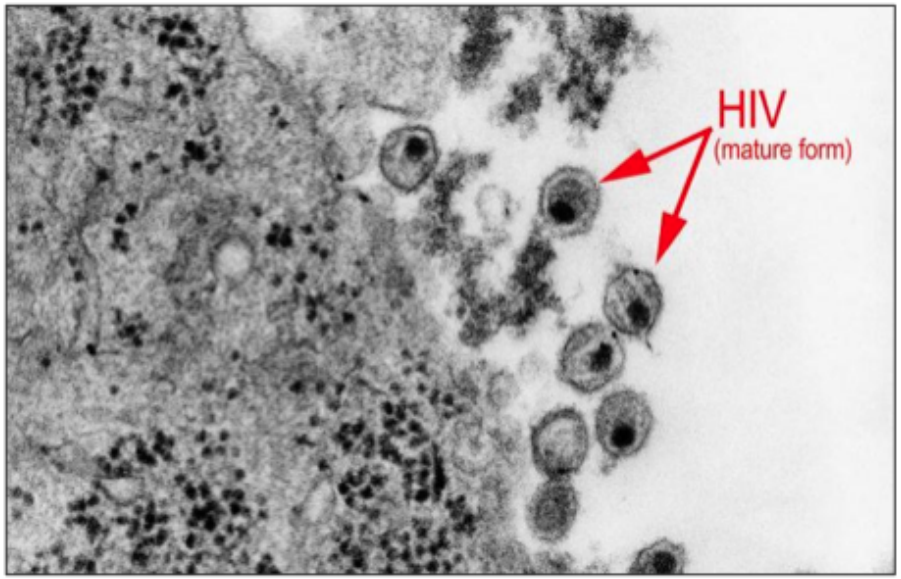


All incident infections verified by second independent specimen;

Discordant results resolved by 3rd independent specimen.

Monitoring

- Aim for maximal virologic suppression ("detectable is unacceptable")
  - HIV RNA < 400 copies / mL after 24 weeks
  - HIV RNA < 20 copies / mL after 48 weeks
- Maintain adequate CD4 count
  - Increases 50-150 cells/mm3 until steady state



Post-exposure prophylaxis (PEP)

- Risk of HIV infection following occupational exposure to HIV-infected blood
  - Approximately 0.3% following percutaneous exposure
  - Approximately 0.09% following mucous membrane exposure

Lessons from Occupational Exposure Literature

- Relative Risk of Infection associated with:
  - Deep injury OR: 16.1
  - Visible blood OR: 5.2
  - Needle in vein/artery OR: 5.1
  - Source is terminally ill OR: 6.4

Factors Associated with Increased Risk

- Visible contamination of device (such as needle) with patient's blood
- Needle having been placed directly into vein or artery
- Hollow-bore (vs solid) needle
- Deep injury
- Source patient with terminal illness
- High viral load
  (not established in occupational exposure)

Not considered infectious for HIV, unless visibly bloody

- Feces
- Nasal Secretions
- Saliva
- Sputum
- Sweat
- Tears
- Urine
- Vomitus

Initiating PEP

- PEP should be started as soon as possible, preferably within hours, rather than days following exposure
- When uncertain as to which drugs to choose, start the basic regimen rather than delay
- PEP should be administered for 4 weeks if tolerated
- Side effects of ARV drugs are common, and a major reason for not completing PEP regimens

Initiating PEP

- Re-evaluate exposed HCP within 72 hours of exposure, especially as additional information about the exposure or source patient becomes available
- If the source is found to be HIV negative, PEP should be discontinued
- Rapid HIV testing of the source patient can facilitate decisions regarding PEP when the source patient's HIV status is unknown

Which Drugs to Use?

- Consultation with an expert is recommended
- Expanded ≥ 3-drug PEP regimens:
  - Preferred:
    - LPV/RTV (Kaletra) + basic 2-drug regimen
  - Alternative:
    - ATV* ± RTV
    - FPV ± RTV
    - IDV** ± RTV
    - SQV + RTV
    - NFV***
    - EFV***

+ basic 2-drug regimen

If ATV is coadministered with TDF, RTV must be included in the PEP regimen.
**Avoid in late pregnancy
***Avoid in pregnancy

Current ARV Medications

- **NRTI**
  - Abacavir (ABC)
  - Didanosine (ddI)
  - Emtricitabine (FTC)
  - Lamivudine (3TC)
  - Stavudine (d4T)
  - Tenofovir (TDF)
  - Zidovudine (AZT, ZDV)
- **NNRTI**
  - Delavirdine (DLV)
  - Efavirenz (EFV)
  - Etravirine (ETR)
  - Nevirapine (NVP)
- **PI**
  - Atazanavir (ATV)
  - Darunavir (DRV)
  - Fosamprenavir (FPV)
  - Indinavir (IDV)
  - Lopinavir (LPV)
  - Nelfinavir (NFV)
  - Ritonavir (RTV)
  - Saquinavir (SQV)
  - Tipranavir (TPV)
- **Integrase Inhibitor (II)**
  - Raltegravir (RAL)
- **Fusion Inhibitor**
  - Enfuvirtide (ENF, T-20)
- **CCR5 Antagonist**
  - Maraviroc (MVC)

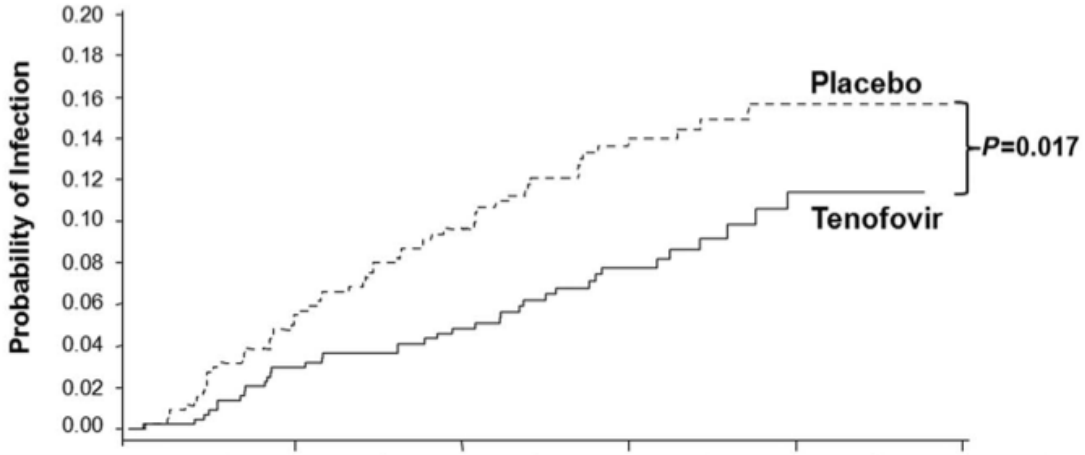
HIV Prevention: Turning the Tide

Adult Male Circumcision

- Reduction in transmission from HIV+ women to HIV – men by 50-60%
  - Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta M, Puren A. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: The ANRS 1265 trial. *PLoS Med 2005;* ***2: 1112–22***
  - Gray RH, Kigozi G, Serwadda D, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. *Lancet* 2007; **369: 657–66.**
  - Bailey RC, Moses S, Parker CB, et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomisedcontrolled trial. *Lancet 2007;* ***369: 643–56.***
- No effect on transmission from HIV+ men to HIV- women

Search for a Microbicide

- CAPRISA 004 (July 2010)
  - Tenofovir intravaginal gel pre and post coitus
  - 39% efficacy (95% CI: 6-60%)
  - Effect on HSV 2



Months of follow-up	6	12	18	24	30
Cumulative HIV endpoints	37	65	88	97	98
Cumulative women-years	432	833	1143	1305	1341
HIV incidence rates (Tenofovir vs Placebo)	6.0 vs 11.2	5.2 vs 10.5	5.3 vs 10.2	5.6 vs 10.2	5.6 vs 9.1
Effectiveness (*P*-value)	**47% (0.064)**	**50% (0.007)**	**47% (0.004)**	**40% (0.013)**	**39% (0.017)**

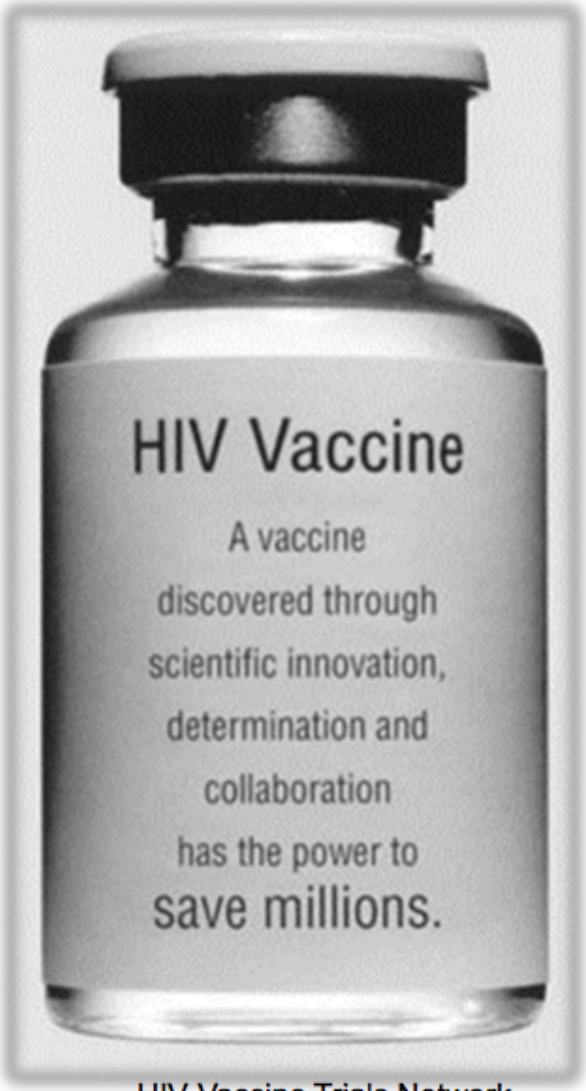
Search for a Microbicide

- Future Directions
  - Dosing Frequency
  - Route
  - Other agents
- What to do with partial efficacy?
  - Impact on prevention research

Nature Biotechnology, 2009

When will an HIV Vaccine be available?

a. A vaccine is available now
b. Next year
c. 5 years
d. 10 years
e. Don’t know



HIV Vaccine Trials Network

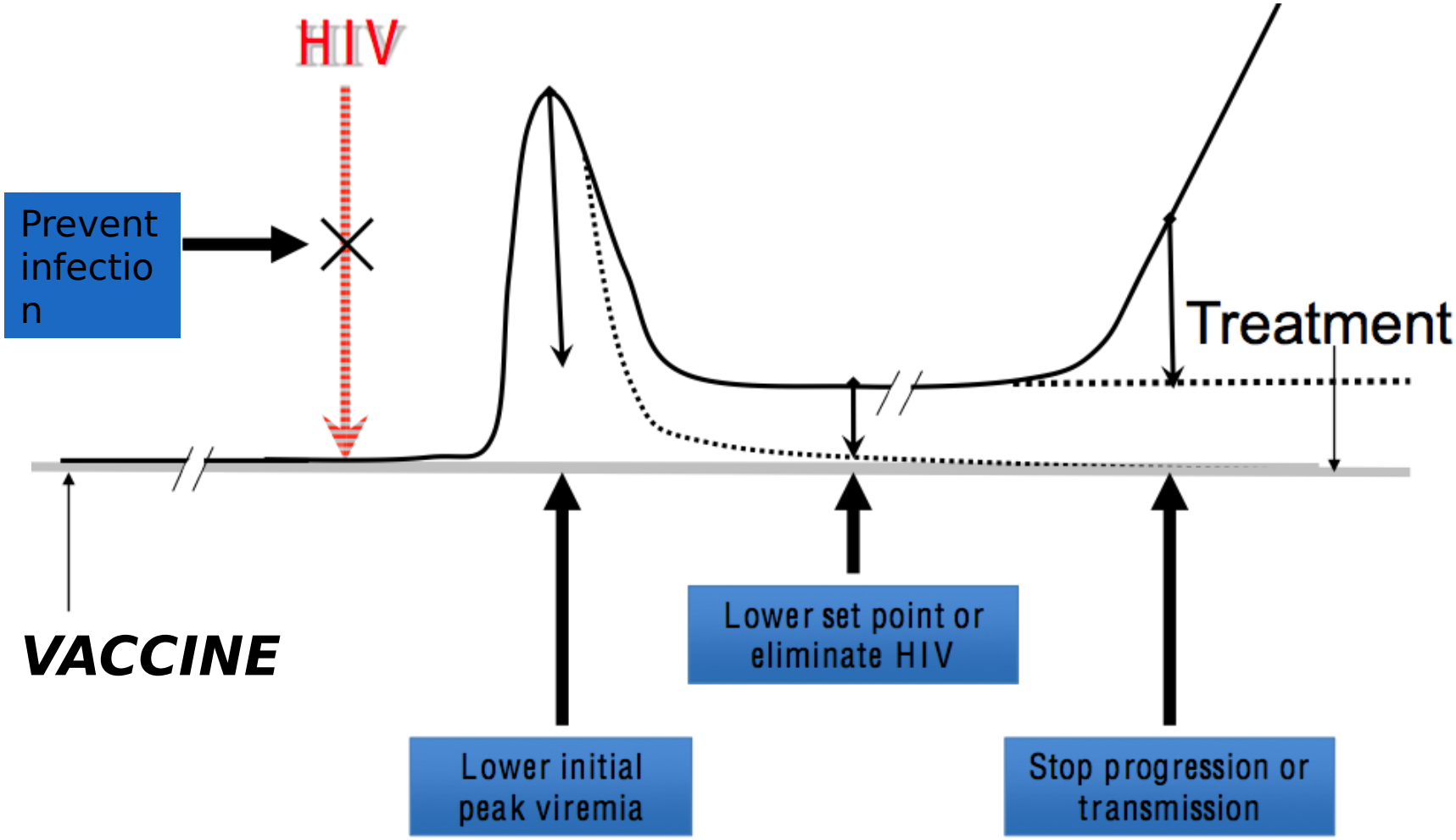
The NEW ENGLAND JOURNAL of MEDICINE

Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand

Supachai Rerks-Ngarm, M.D., Punnee Pittisutthithum M.D., D.T.M.H., Sorachai Nitayaphan, M.D., Ph.D., Jaranit Kaewkungwal Ph.D., Joseph Chiu, M.D., Robert Paris, M.D., Nakorn Premsri, M.D., Chawetsan Namwat, M.D., Mark de Souza, Ph.D., Elizabeth Adams, M.D., Michael Benenson, M.D., Sanjay Gurunathan, M.D., Jim Tartaglia, Ph.D., John G. McNeil, M.D., Donald P. Francis, M.D., D.Sc., Donald Stablein, Ph.D., Deborah L. Birx, M.D., Supamit Chunsuttiwat, M.D., Chirasak Khamboonruang, M.D., Prasert Thongcharoen, M.D., Ph.D., Merlin L. Robb, M.D., Nelson L. Michael, M.D., Ph.D., Prayura Kunasol, M.D., and Jerome H. Kim, M.D., for the MOPH–TAVEG Investigators*

NEJM 361:2209 (03 Dec 09)

HIV/AIDS Vaccine Mechanisms



HIV Vaccine Strategies

DNA

Peptides

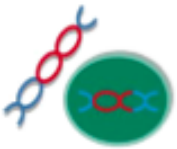
Subunits

Live Vectors

Dendritic Cells

Virus-like Particles/Pseudoviri ons

+/- Adjuvants



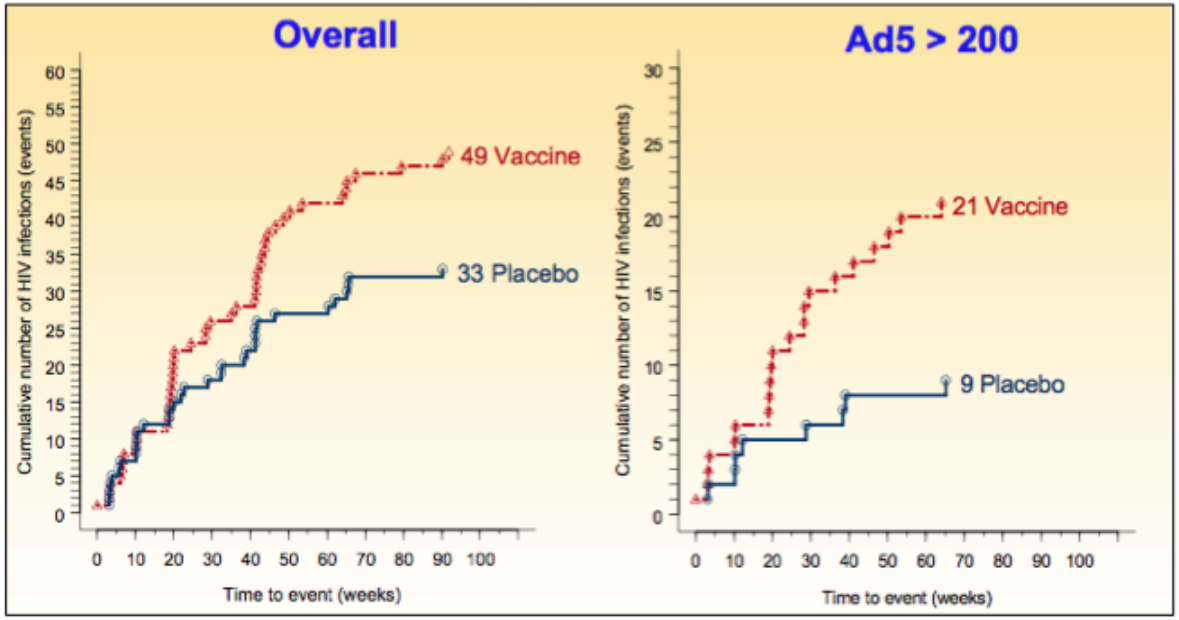
Combinations

Whole Killed HIV

Live Attenuated HIV

Step Study

- 3,000 high-risk, uninfected participants
- Ad5 vectored vaccine x 3
- Stopped early because no evidence of efficacy
- More infections among vaccinees
  - Risk related to pre-existing Ad titer, circumcision



Buchbinder, 2008

HR = 1.2 [95% CI 0.6-2.2]

HR = 2.3 [95% CI 1.2-4.3]

RV144

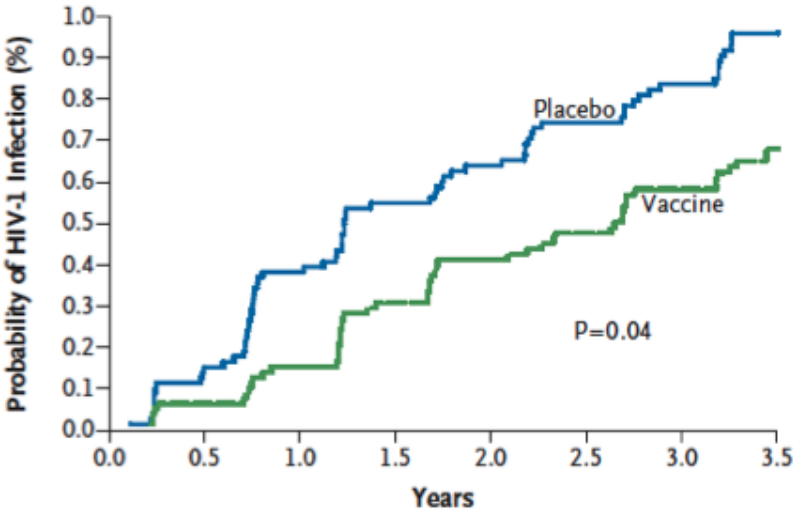
- Modest results, but first sign of protection in humans
  - N=16,000 Thai volunteers at community risk
  - Canarypox vector x 4 + gp120 x 2
  - Modified intention to treat efficacy 31.2% (95% CI, 1.1 to 52.1; P = 0.04)
  - No effect on viral load

The NEW ENGLAND JOURNAL of MEDICINE

Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand

Supachai Rerks-Ngarm, M.D., Punnee Pittisuttithum M.D., D.T.M.H., Sorachai Nitayaphan, M.D., Ph.D., Jaranit Kaewkungwal Ph.D., Joseph Chiu, M.D., Robert Paris, M.D., Nakorn Premsri, M.D., Chawetsan Namwat, M.D., Mark de Souza, Ph.D., Elizabeth Adams, M.D., Michael Benenson, M.D., Sanjay Gurunathan, M.D., Jim Tartaglia, Ph.D., John G. McNeil, M.D., Donald P. Francis, M.D., D.Sc., Donald Stablein, Ph.D., Deborah L. Birx, M.D., Supamit Chunsuttiwat, M.D., Chirasak Khamboonruang, M.D., Prasert Thongcharoen, M.D., Ph.D., Merlin L. Robb, M.D., Nelson L. Michael, M.D., Ph.D., Prayura Kunasol, M.D., and Jerome H. Kim, M.D., for the MOPH–TAVEG Investigators*

Modified Intention-to-Treat Analysis



Coming Steps

- Improved antiretroviral microbicides
- Test and treat
- Extend the impact of RV 144
- New generation HIV vaccines

THANK YOU

QUESTIONS?

References

- UNAIDS Report on the Global AIDS Epidemic www.unaids.org/en/KnowledgeCentre/HIVData/GlobalReport/2 008/default.asp

- DHHS Guidelines for Use of ART in Adults and Adolescents www.aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx? Guidelin eID=7

- Military HIV Research Program www.hivresearch.org/home.php

- International AIDS Vaccine Initiative www.iavi.org/Pages/home.aspx

- STEP paper: Buchbinder et al. Lancet, 2008

- RV144 Thai Trial Paper: Rerks-Ngarm et al, NEJM, 2009